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Tobacco Smoke, Indoor Air Pollution and Tuberculosis: A Systematic Review and Meta-Analysis

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Abbreviations: AM, alveolar macrophage; CI, confidence interval; IAP, indoor air pollution from biomass fuels; OR, odds ratio; TB, tuberculosis; TST, tuberculin skin test

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ABSTRACT

Background

Tobacco smoking, passive smoking, and indoor air pollution from biomass fuels have been implicated as risk factors for tuberculosis (TB) infection, disease, and death. Tobacco smoking and indoor air pollution are persistent or growing exposures in regions where TB poses a major health risk. We undertook a systematic review and meta-analysis to quantitatively assess the association between these exposures and the risk of infection, disease, and death from TB.

Methods and Findings

We conducted a systematic review and meta-analysis of observational studies reporting effect estimates and 95% confidence intervals on how tobacco smoking, passive smoke exposure, and indoor air pollution are associated with TB. We identified 33 papers on tobacco smoking and TB, five papers on passive smoking and TB, and five on indoor air pollution and TB. We found substantial evidence that tobacco smoking is positively associated with TB, regardless of the specific TB outcomes. Compared with people who do not smoke, smokers have an increased risk of having a positive tuberculin skin test, of having active TB, and of dying from TB. Although we also found evidence that passive smoking and indoor air pollution increased the risk of TB disease, these associations are less strongly supported by the available evidence.

Conclusions

There is consistent evidence that tobacco smoking is associated with an increased risk of TB. The finding that passive smoking and biomass fuel combustion also increase TB risk should be substantiated with larger studies in future. TB control programs might benefit from a focus on interventions aimed at reducing tobacco and indoor air pollution exposures, especially among those at high risk for exposure to TB.

The Editors' Summary of this article follows the references.



Introduction

Tuberculosis (TB) causes an estimated 2 million deaths per year, the majority of which occur in the developing world. Many studies conducted over the past 60 years have found an association between tobacco smoking and TB, as manifested by a positive tuberculin skin test (TST) or as active disease and its sequelae. A smaller number have found that indoor air pollution from biomass fuels (IAP) and passive smoking are also risk factors for TB and its sequelae. Tobacco smoking has increased substantially in developing countries over the past three decades, with an estimated 930 million of the world's 1.1 billion smokers currently living in the low-income and middle-income countries [1,2]. Approximately half of the world's population uses coal and biomass, in the form of wood, animal dung, crop residues, and charcoal as cooking and heating fuels especially in Africa and Asia. Given the persistent or growing exposure to both smoking and IAP in regions where TB poses a major health risk, it is essential to delineate the role of these environmental factors in the etiology and epidemiology of TB. Previous reviews have addressed qualitatively the epidemiologic and biologic link between tobacco smoke and TB, but have not systematically reviewed the epidemiologic data on this association [3,4]. We therefore undertook to quantitatively assess the association between smoking, passive smoking, and IAP, and the risk of infection, disease, and death from TB. We have considered smoking, passive smoking, and IAP together because these sources result in exposure to common set of respirable pollutants, and because their effects are currently or increasingly found in the developing countries.

Methods

Data Source

We searched the PubMed via the NCBI Entrez system (1950 to February 1, 2006) (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) and the EMBASE via Ovid (1988 to 2003) (<http://www.ovid.com>) for studies of the association between smoking, passive smoking, and indoor air pollution and TB infection, disease, and mortality. We also searched bibliographies of identified reports for additional references. Our search strategy is described in Box 1.

Study Selection

We limited our search to studies published in English, Russian, and Chinese. Studies were included if they involved human participants with TB or at risk from TB. We included studies if a quantitative effect estimate of the association between ever, former, or current tobacco smoking, passive smoking, or IAP, and TST positivity, clinical TB disease, or TB mortality was presented or could be estimated from the data provided in the paper or through contact with the authors. Studies were included in the review if they were full-length peer-reviewed reports of cohort studies, case-control studies, or cross-sectional studies, if they controlled for possible confounding by age or age group, and if they screened for the presence of TB among exposed and unexposed study participants in the same way. For analyses of the effect of passive smoking on TB outcomes, we excluded studies if they did not restrict the population under study to nonsmokers. If multiple published reports from the same study participants

Box 1. Search Strategy and Terms Used to Identify Studies on Smoking and TB

MeSH term search

1. "tuberculosis"
2. "smoking"
3. "air pollution, indoor"
4. "biomass"
5. "fuel oils"
6. "(1) AND (2)" OR "(1) AND (3)" OR "(1) AND (4)" OR "(1) AND (5)"

Direct keyword search:

7. "tuberculosis"
8. "smoking"
9. "indoor air pollution"
10. "cooking fuel"
11. "biomass"
12. "(7) AND (8)" OR "(7) AND (9)" OR "(7) AND (10)" OR "(7) AND (11)"
13. (6) OR (12)

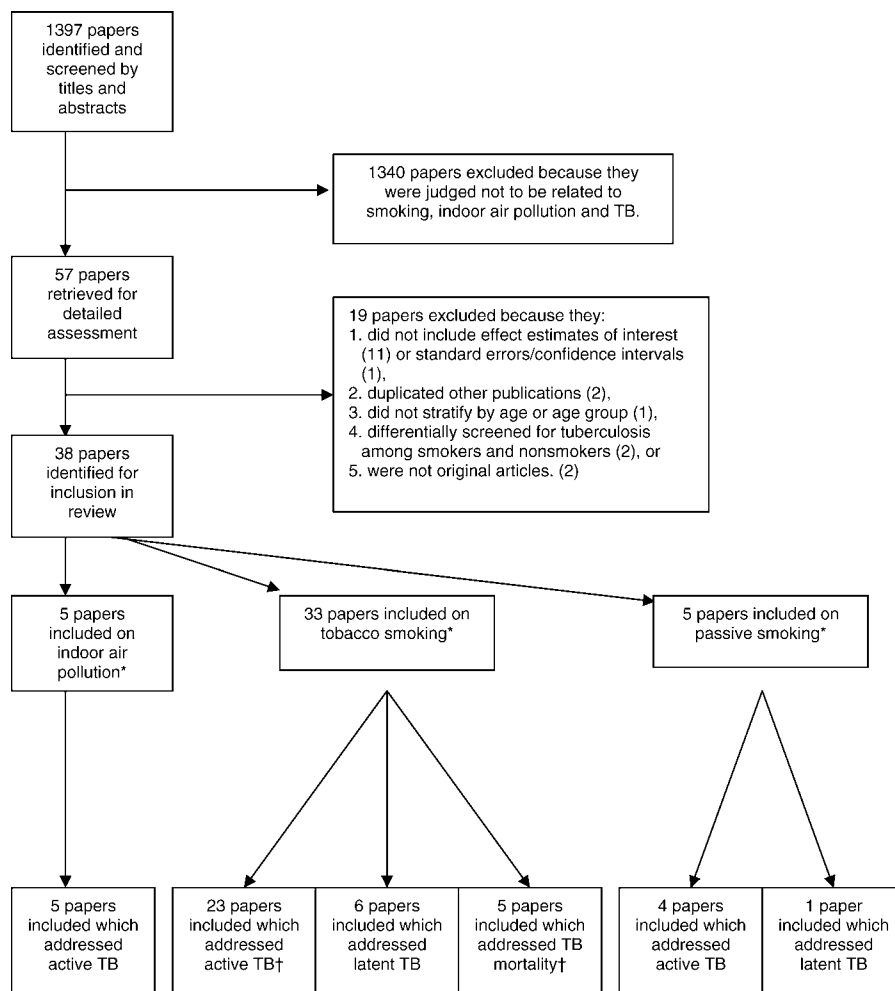
were available, we included only the one with the most detailed information for both outcome and exposure.

Data Extraction and Quality Assessment

For every eligible study, we collected detailed information on year and country of study, study design, study population, sample size, choice of controls, definition and measurement of tobacco smoking or IAP, type of TB outcome, confounders adjusted for, effect sizes and 95% confidence intervals (CIs), and dose-response relationships. Since TB disease and death are relatively rare events, even in high-incidence areas, we assumed that odds ratios (ORs), risk ratios, and rate ratios all provided an equivalent estimate of risk and therefore reported them as ORs [5]. Although latent TB infection is not a rare event, each of the studies of latent TB infection estimated ORs and we therefore reported ORs for this outcome as well. Data were extracted independently by two of the investigators (HL and MM), and differences were resolved by discussion with a third (ME).

Data Synthesis

We performed separate analyses for each exposure-outcome association that had been studied. Within each subanalysis we further stratified on different study designs. When more than one study used a specific study design, we assessed heterogeneity using the I^2 statistic described by Higgins et al. [6]. Because of the significant heterogeneity and different study designs within subgroups, we did not compute pooled effect measures [7]. Instead, we graphically presented each of the weighted point estimates and 95% CIs of effect estimates for individual studies within subanalyses. For the subanalysis in which we found no significant heterogeneity, effect estimates were given a weight equal to the inverse variance of the study (fixed effects model). For those subanalyses in which we noted significant heterogeneity, we used a random effects model to assign the weight of each study according to the method described by DerSimonian and Laird [8]. In order to assess the effect of study quality on the reported effect estimates, we conducted sensitivity analyses in which we compared pooled effect estimates for subgroups stratified on quality-associated study characteristics including study design (cohort, case-control or cross-sectional), type of control selection (population based or



* 3 papers addressed both indoor air pollution and tobacco smoking; 2 papers addressed both passive smoking and tobacco smoking
 † 1 paper addressed both active TB and TB mortality

Figure 1. Flow Diagram of Study Steps and Exclusions
 doi:10.1371/journal.pmed.0040020.g001

other), adjustment for important potential confounder (alcohol and socioeconomic status), and outcome classification (microbiological or other). We considered studies to be of higher quality if they (1) were cohort studies, (2) were case-control studies using population-based controls, (3) adjusted for important confounders, (4) classified the outcome on the basis of microbiological findings, and (5) restricted the outcome to pulmonary TB. As above, pooled estimates were calculated using a fixed effects model if there was no significant heterogeneity and a random effects models for those subanalyses in which we found heterogeneity.

We tested for possible publication bias using Begg's and Egger's tests and by visual inspection for asymmetry of a plot of the natural logarithms of the effect estimates against their standard errors according to method described by Begg [9,10]. Several large studies on smoking and TB mortality had highly variable results and thus fell outside the lines of the funnel plot. Therefore, we conducted a sensitivity analysis in which we repeated the funnel plot excluding all of the mortality studies. All statistical procedures were carried out in Intercooled Stata Version 8.2 (Stata, <http://www.stata.com>).

Results

We identified and screened 1,397 papers by titles and abstracts. We excluded 1,340 papers because they were judged not to be related to smoking, IAP, and TB. The remaining 57 articles were obtained for detailed review; 19 of these were excluded because the same studies were published in different journals [11,12], the effect sizes and CIs of interest were not reported or could not be estimated [13–24], there were severe flaws in study design [25–27], or the article was not original [28,29]. Thirty-eight papers were included in the final analysis. Figure 1 delineates the exclusion process and Table 1 summarizes the studies that were included in the final analysis.

Tobacco Smoking and Latent TB Infection

Figure 2 shows the risk of latent TB among smokers compared with nonsmokers in six studies [30–35] on tobacco smoking and latent infection. The studies were conducted in five countries: the US, Spain, South Africa, Pakistan, and Vietnam. Although the timing of smoking (current, former,

Table 1. Study Characteristics

Category	Type of Study	Study	Location	Population/Setting	Exposure	Outcome (Number of Cases)	Adjusted Variables	Findings
Tobacco smoking and latent infection	Case-control studies	Anderson et al. 1997 [35]	United States	293 incarcerated adults	Current tobacco smoking	TST conversion: >10 mm or >5 mm if HIV+ (n = 116)	Age, living conditions, gender, alcohol, HIV, contact with TB patient, BMI	Smoking before and after incarceration associated with conversion, dose response observed for both duration and quantity
	Cross-sectional studies	den Boon et al. 2005 [30]	South Africa	2,401 population-based adults, HIV prevalence 12%	Ever tobacco smoking	TST >10 mm (n = 1,832)	Age, gender, SES, BMI	Smoking associated with TST+, dose response observed based on pack years
		Hussain et al. 2003 [31]	Pakistan	425 incarcerated men	Current tobacco smoking	TST >10 mm if BCG unvaccinated, >15 mm in BCG vaccinated (n = 225)	Age, living conditions, SES, BCG	Smoking associated with TST+ with dose response observed based on quantity
		Plant et al. 2002 [32]	Vietnam	1,395 adult prospective migrants	Ever tobacco smoking	TST >5 mm (n = 898); >10 mm (n = 611); >15 mm (n = 260)	Age, gender, contact with TB patient, living conditions, SES	Smoking associated with TST+ for all cutoffs, but strength of association declined with increasing cut-off
Tobacco smoking and TB disease		Solsona et al. 2001 [33]	Spain	447 residents of homeless shelter	Current smoker of >10 cigarettes per day	TST >5 mm (n = 335)	Age, gender, alcohol, BCG vaccination	Smoking and age, but not alcohol, associated with TST+
		McCurdy et al. 1997 [34]	United States	296 adult and child Hispanic migrant farm workers	Current and former tobacco smoking	TST >10 mm (n = 49)	Age, gender, SES	Former smoking more strongly associated with TST+ than current
	Cohort studies	Leung et al. 2004 [57]	Hong Kong	42,655 clients of the Elderly Health Services of Hong Kong	Current and former tobacco smoking	Pulmonary and extrapulmonary TB confirmed by bacteriology or by clinical, CXR, or histologic grounds (n = 252)	Age, gender, alcohol, SES, living conditions, comorbidities	Current smoking associated with pulmonary but not extrapulmonary TB; dose response observed based on quantity
	Case-control studies	Shetty et al. 2006 [42]	India	189 TB adult outpatients and 189 controls who were relatives of non-TB patients	Current and former tobacco smoking and use of biomass cooking fuels	Pulmonary TB diagnosed according to national TB Control Program guidelines (n = 252)	Age, gender, SES, living conditions, alcohol, comorbidities, tobacco smoking, biomass fuel use	Former smoking, but not current smoking or use of biomass fuels, associated with disease
		Jick et al. 2006 [46]	United Kingdom	497 patients and 1,966 controls from General Practice Research Database	Current and former tobacco smoking	All TB as defined by having received at least three anti-TB medications for at least 6 mo	Age, gender, region, BMI, comorbidities	Current but not former smoking associated with disease
		Lienhardt et al. 2005 [40]	The Gambia, Guinea Conakry, Guinea Bissau	822 West African patients, 687 household controls, 816 community controls	Current and former smoking	Pulmonary TB confirmed by sputum smear positivity	Age, gender, contact with TB patient, alcohol, BCG vaccination, comorbidities	Current and former smoking associated with disease and dose effect reported based on duration of smoking
		Wang et al. 2005 [47]	China	158 adult patients and 316 neighborhood controls	Tobacco smoking	Pulmonary TB diagnosed by smear sputum positivity	Age, gender, SES	Ever smoking associated with disease; dose effect observed for quantity

Table 1. Continued

Category	Type of Study	Study	Location	Population/Setting	Exposure	Outcome (Number of Cases)	Adjusted Variables	Findings
		Crampin et al. 2004 [48]	Malawi	598 adult patients and 992 community-based controls	Former smoking and smoking prior to onset of illness, cooking fire exposure (indoor and outdoor)	All culture-confirmed and probable cases of TB for which at least one sputum smear or culture was positive	Age, gender, region, HIV	Former smoking and smoking more than five cigarettes per day, but not exposure to cooking fires, associated with disease; nonsignificant dose effect observed for quantity
		Ariyothai et al. 2004 [55]	Thailand	100 adult inpatients and 100 controls from outpatient or inpatient department of same hospital	Current (up to 6 mo prior to diagnosis) and former smoking and passive smoke	Pulmonary TB diagnosed by bacteriology and/or by CXR and histologic grounds	Age, alcohol, living conditions, contact with TB patient, BMI, BCG scar	Association with both current and former smoking; dose effect observed based on duration and quantity; association with passive smoke noted
		Leung et al. 2003 [41]	Hong Kong	851 patients from TB registry, 7,835 controls from General household survey	Ever tobacco smoking	All TB confirmed by bacteriology or by clinical, CXR, or histologic grounds	Age, gender, alcohol	Ever smoking associated with disease; effect partly reduced by restricting analysis to nondrinkers
		Kollapan et al. 2002 [49]	India	112 adult male patients and 553 community-based controls from the same villages	Tobacco smoking including cigarettes and "beedi"	Pulmonary TB diagnosed by culture or sputum positivity	Age	Smoking associated with disease; dose effects observed for both quantity and duration of smoking
		Tekkel et al. 2002 [50]	Estonia	248 adult inpatients and 248 controls from Estonia Population Registry	Current and former tobacco smoking and passive smoke	Pulmonary TB diagnosed according to WHO European guidelines	Age, gender region, SES	Strong association with disease for both former and current smoking
		Tocque et al. 2001 [51]	United Kingdom	112 adult patients and 198 controls from regional general practitioner databases	Current, ever and 2 years prior to diagnosis or interview smoking	All TB diagnosed by bacteriology	Age, gender, SES, contact with TB patient, race, comorbidities	Smoking more than 30 y associated with disease but other forms of smoking were not
		Dong et al. 2001 [53]	China	174 adult patients from TB registry and 174 community-based controls	Smoking and passive smoking	Pulmonary TB diagnosed by sputum positivity	Age, gender, region, contact with TB patient, SES, living conditions, alcohol, dust exposure, BMI, BCG vaccination	Nonsignificant association with both smoking and passive smoking; dose response observed on basis of quantity
		Gupta et al. 2001 [52]	India	200 adult patients from hospital or chest clinic, 200 chest clinic controls, and 200 healthy controls	Ever smoking (More than 400 lifetime cigarettes)	Pulmonary TB diagnosed by sputum positivity or by CXR and treatment response	Age, gender, contact with TB patient, SES	Strong association with smoking compared to both sets of controls; dose response observed on basis of cumulative exposure but not current quantity
		Alcaide et al. 1996 [54]	Spain	46 adult patients and 46 TST positive controls	Current smoking (non-smoker defined as not smoking within past 6 mo) and passive smoking	Pulmonary TB diagnosed by sputum positivity or by clinical, CXR, and epidemiological evidence and positive TST	Age, gender SES	Strong association with smoking; dose effect observed based on quantity of cigarettes smoked

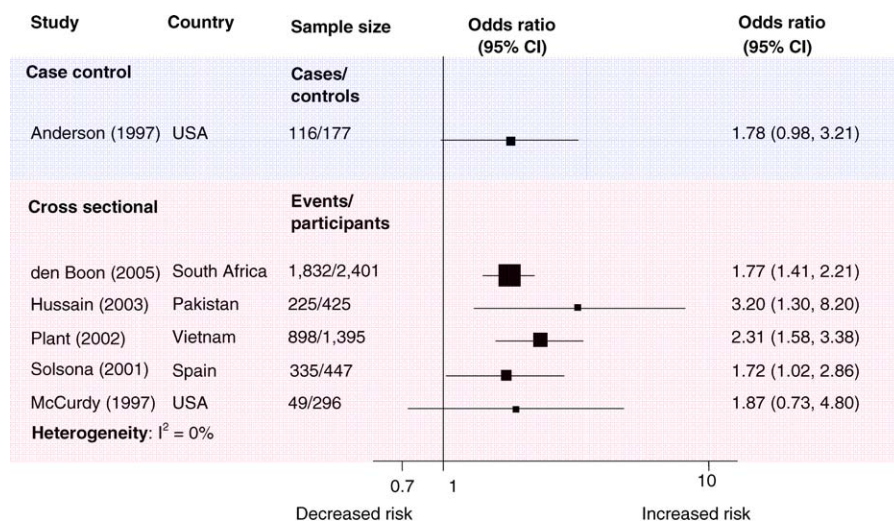
Table 1. Continued

Category	Type of Study	Study	Location	Population/Setting	Exposure	Outcome (Number of Cases)	Adjusted Variables	Findings
		Buskin et al. 1994 [43]	United States	151 adult outpatients and 545 controls who screened negative for TB at a county TB clinic	Current and former tobacco smoking	All TB diagnosed on the basis of US CDC criteria	Age, gender, alcohol, SES, race, BMI, HIV	Nonsignificant association between both current and former smoking and disease; dose response observed for duration but not quantity of smoking
		Lewis et al. 1963 [44]	United Kingdom	100 inpatient adult male patients and 100 adult male controls hospitalized for other diseases	Tobacco smoking 6 mo prior to diagnosis	Pulmonary TB diagnosed by bacteriology	Alcohol	No effect of smoking after stratification for alcohol; control illnesses may also have been associated with smoking
		Brown et al. 1961 [45]	Australia	100 inpatients and 100 controls hospitalized on surgical service (all male ex-servicemen)	Tobacco smoking	Probable pulmonary TB; diagnostic method not specified	Alcohol	No effect of smoking after stratification for alcohol; control illnesses may also have been associated with smoking
		Lowe 1956 [56]	United Kingdom	1,200 adult patients (434 inpatients and 766 outpatients) and 979 controls (588 minor trauma outpatients and 391 surgical inpatients)	Current smoking	All TB identified through notification data; method of diagnosis unknown	Age, gender	Association with current smoking and disease; dose response observed based on quantity
	Cross-sectional studies	Gajalakshmi et al. 2003 [2]	India	235,101 urban men	Ever smoking	Pulmonary tuberculosis by self-report (n = 1,122)	Age, SES, chewing tobacco	Strong association between ever smoking and TB; dose response observed based on quantity
		Gupta et al. 1997 [36]	India	543 rural and 164 urban adults	Smoking and use of wood or cowdung cakes for fuel	Pulmonary tuberculosis diagnosed by radiology, history, clinical exam and sputum examination	Age	Association between both use of biomass for fuel (significant) and smoking (nonsignificant) and tuberculosis
		Yu et al. 1988 [37]	China	30,289 adult residents of Shanghai	Smoking	Pulmonary tuberculosis diagnosed by a physician; criteria for diagnosis not stated (n = 202)	Age, gender, contact with TB patient, region, SES	Association between smoking and tuberculosis with increasing effect at higher dose as ascertained by quantity
		Adelstein et al. 1967 [38]	United Kingdom	76,589 adult volunteers from factories, offices, or general public	Current and former smoking	Pulmonary TB identified by MMR and confirmed by physician (n = 96)	Age, gender	Association between both current and former smoking; dose response observed for quantity
Tobacco smoking and TB mortality	Cohort studies	Shah et al. 1959 [39]	India	439 employees	Smoking	Pulmonary TB identified by MMR and confirmed by physician (n = 46)		Association between smoking and disease
		Gupta et al. 2005 [61]	India	99,570 >35-year-olds from Mumbai voter list	Ever smoking (over 95% current)	Death from TB after 5.5 y of follow-up; diagnosis based on municipal corporation records (n = 544)	Age, SES, gender	Association between smoking and death from TB but stronger in women than men

Table 1. Continued

Category	Type of Study	Study	Location	Population/Setting	Exposure	Outcome (Number of Cases)	Adjusted Variables	Findings
	Case-control studies	Sitas et al. 2004 [58]	South Africa	414 patients and 1,124 controls who died of nonsmoking-related causes and were over 25 years of age	Smoking 5 y prior to death	Death from TB as listed on death notification form based on ICD-10	Age, gender, SES, race	Association between smoking and death from TB
		Gajalakshmi et al. 2003 [2]	India	3,369 male patients and 29,851 male controls living in a household where a female member has died	Ever smoking	Death from pulmonary TB based on data from Vital Statistics Department supplemented by family interview	Age, SES, tobacco chewing	Association between smoking and death from TB for both rural and urban participants
		Lam et al. 2001 [59]	Hong Kong	197 patients from Hong Kong death registry and 13,054 live controls (usually relatives of dead patients)	Having ever smoked 10 y prior to death	Death from pulmonary TB as listed on death certificate based on ICD-9	Age, gender, SES	Association between smoking and death from TB for men but indeterminate in women; dose response observed for quantity
Passive smoking and TB		Liu et al. 1998 [60]	China	12,166 patients and 87,315 controls who died of nonsmoking-related causes	Having ever smoked 6 y or more before death	Death from pulmonary TB based on data from local administrative records and supplemented by review of medical records and discussion with local health workers, community leader, and family	Age, gender, region, urban versus rural	Weak association between smoking and death from TB for both men and women; dose response observed for quantity
		Tipayamongkolgul et al. 2005 [62]	Thailand	130 inpatient child patients and 130 controls attending orthopedic clinic	Distant, close and very close passive smoking as reported by parents	All tuberculosis; diagnostic methods not described	Gender	Close and very close exposure (but not distant) strongly associated with TB
		Altet et al. 1996 [63]	Spain	93 patients and 95 controls from among TST+ children exposed to a household member with tuberculosis	Passive smoking over 6 mo prior to study as reported by parents	Pulmonary TB diagnosed by bacteriology or CXR, clinical evidence, and TST+	Age, gender, SES, BCG	Passive smoking strongly associated with TB; with increasing risk among those exposed both within and out of the home and among younger children
Indoor air pollution and TB disease	Cross-sectional study on latent infection	Singh et al. 2005 [64]	India	281 children contacts of adults with pulmonary TB	Exposure to smoking as reported by parents	TST >10 mm (n = 95)	Age, BCG, malnutrition, smear status of contact	Exposure to smoking associated with TB
	Case-control studies (see also [42,48])	Perez-Padilla et al. 2001 [66]	Mexico	288 patients and 545 controls with ear, nose, and throat diagnoses	Current and former use of biomass fuels, number of years cooking with biomass stoves, Current use of biomass fuels	Pulmonary TB diagnosed by bacteriology	Age, gender, region, living conditions, SES, tobacco smoking	Exposure to biomass fuels associated with TB
	Cross-sectional studies (see also [36])	Mishra et al. 1999 [65]	India	260,162 adults sampled in India's National Family Health survey		All tuberculosis identified by self-report	Age, gender, race, urban versus rural, SES, region	Exposure to biomass fuels associated with TB

BCG, bacille Calmette-Guérin vaccine; BMI, body mass index; CXR, chest x-ray; SES, socioeconomic status.
doi:10.1371/journal.pmed.0040020.t001



Note: The horizontal axis is on log scale

Figure 2. Risk of Latent TB Infection for Smoking Compared with Nonsmoking
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and ever) in relation to the study varied, we did not differentiate between these reported exposures, because the actual time of TB infection was unknown. There was only one case-control study; for the five cross-sectional studies that were included, we found minimal heterogeneity ($I^2 = 0\%$). We also stratified studies that used different cutoffs for the TST; among those analyses that used induration size of 5 mm as the cutoff for a positive test [32,33], the pooled OR for latent TB was 2.08 (95% CI, 1.53–2.83), while among those that used a 10 mm cutoff [30,31,34,35], the pooled OR was 1.83 (95% CI, 1.49–2.23). When we stratified on other quality-associated study characteristics, we found that ORs for TB infection were lower among studies that adjusted for alcohol (Table 2), but that a positive effect of smoking on latent TB remained.

Table 2. Quality Assessment and Subgroup Analysis: Tobacco Smoking and Latent TB Infection

Category	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	I^2
TST cutoff	5 mm (2)	2.08	1.53–2.83	0%
	10 mm (4)	1.83	1.49–2.23	0%
Adjustment for alcohol	Yes (2)	1.76	1.43–2.16	0%
	No (4)	2.20	1.65–2.93	0%
Adjustment for socioeconomic status	Yes (4)	1.94	1.61–2.33	0%
	No (2)	1.75	1.18–2.58	0%
Type of study	Case control (1)	1.78	0.98–3.22	NA
	Cross sectional (5)	1.91	1.60–2.27	0%
Type of smoking	Current smoking (4)	1.91	1.36–2.67	0%
	Ever smoking (2)	1.93	1.51–2.47	28.4%

Not applicable (NA) indicated as appropriate; I^2 statistics can be computed only when there is more than one study.

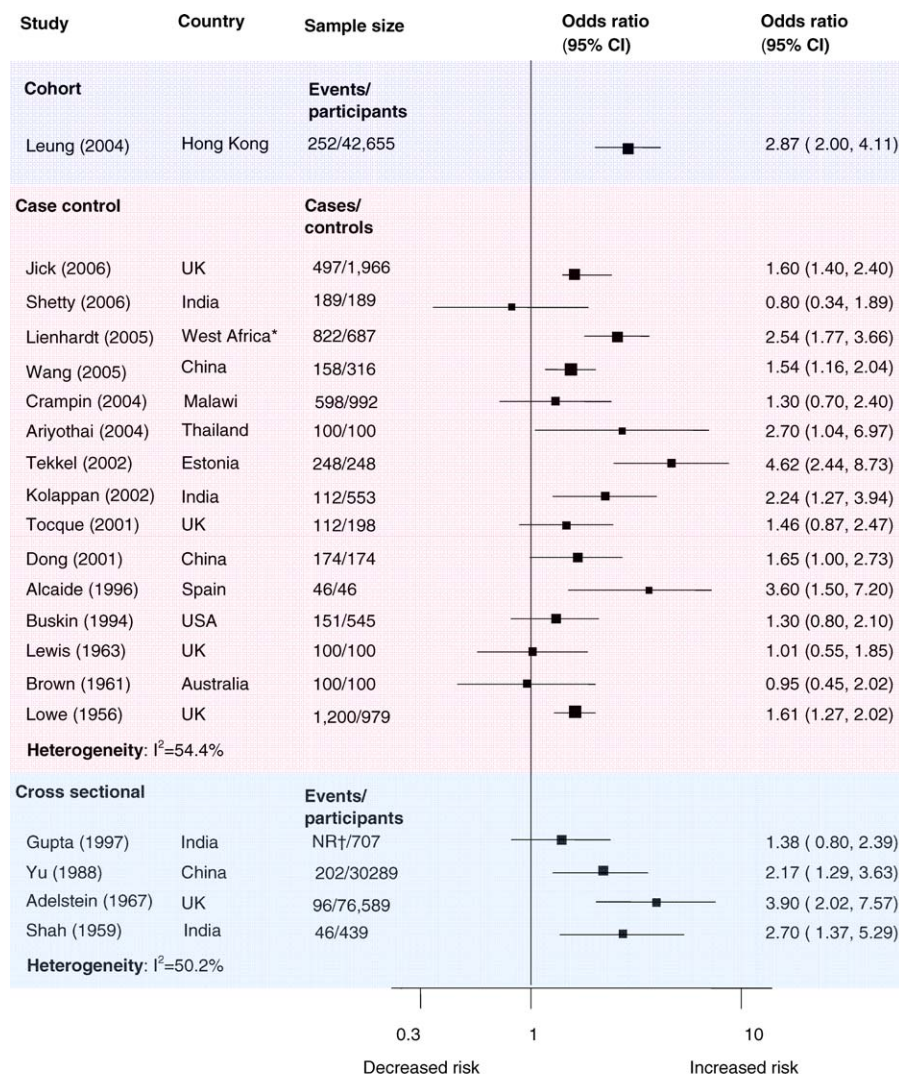
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Tobacco Smoking and Clinical TB Disease

The 23 studies that we identified on the association between tobacco smoking and clinical TB disease were conducted in 12 countries: China/Hong Kong, India, The Gambia, Guinea Conakry, Guinea Bissau, US, UK, Australia, Malawi, Estonia, Spain, and Thailand [2,36–57]. Figures 3–5 shows the risk of clinical TB among current, former, and ever smokers, respectively, compared to nonsmokers for the individual studies. Given the significant heterogeneity among each of these effect estimates, we do not report pooled estimates within each of these three categories; rather, we stratified on important study characteristics within each category for the purpose of sensitivity analysis (Table 3). These analyses show that there was a significantly increased risk of clinical TB among smokers regardless of outcome definition (pulmonary TB versus any TB), adjustment for alcohol intake or socioeconomic status, type of study, or choice of controls. Although stratification by these study-specific variables did not fully explain the variability between studies, heterogeneity was partially accounted for by outcome (pulmonary versus any TB) and by adjustment for alcohol intake. As might be predicted on the basis of biological plausibility, we found a higher risk of clinical TB among smokers when we restricted the analyses to studies that included only cases of pulmonary disease. However, the differences between the effect estimates for pulmonary TB and those for any TB were not statistically significant.

Tobacco Smoking and TB Mortality

We identified five studies on tobacco smoking and TB mortality in adults [2,58–61], conducted in India, South Africa, and China/Hong Kong. Although all of the studies found a positive association between smoking and TB mortality (Figure 6), there was substantial heterogeneity ($I^2 = 98.5\%$ among case-control studies) and a five-fold difference between the most extreme effect estimates. We therefore do not report a pooled estimate for this analysis. A dose-



Note: The horizontal axis is on log scale

* The Gambia, Guinea Conakry, Guinea Bissau

† NR: not reported

Figure 3. Risk of Clinical TB Disease for Current Smoking Compared with Nonsmoking
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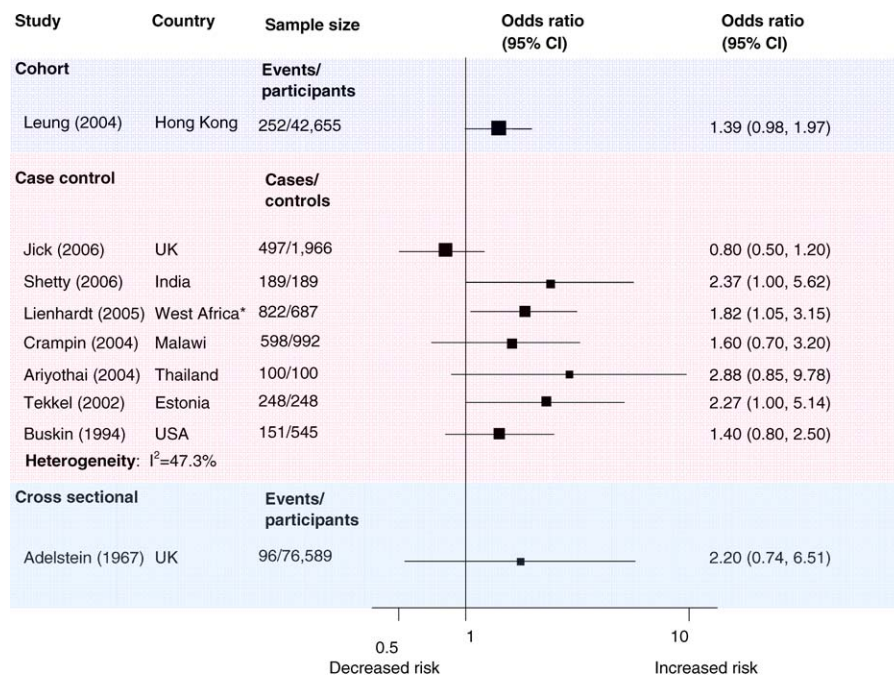
response relation was noted in the two [59,60] studies that stratified on dose. When we conducted a sensitivity analysis excluding the study conducted in India where TB may have been differentially overdetected among smokers [2,61], heterogeneity was markedly reduced ($I^2 = 38.6\%$). Other sensitivity analyses are demonstrated in Table 4.

Passive Smoking and TB

We identified five studies on passive smoking and TB, of which four were case-control studies assessing the risk of clinical TB [50,53–55,62,63] and one a cross-sectional study on the risk of latent infection [64]. Two studies did not exclude active smokers while assessing passive smoking and were, therefore, not included in the analysis of passive smoking and TB [50,53]. Figure 7 shows the individual effect measures for the studies on active disease; each found a positive association between passive smoking and TB. The

heterogeneity among the studies was largely explained by the age of the participants; the risk of TB among children exposed to passive smoking was significantly higher than it was among adults ($p = 0.002$), and there was no remaining heterogeneity within the subgroups stratified by age. The single study examining the risk of latent TB infection among those exposed to passive smoking reported an OR of 2.68 (95% CI, 1.52–4.71) [64]. Sensitivity analyses for these estimates are given in Table 5.

A dose response was found in both of the two studies that stratified on exposure intensity; one found that TB risk increased with the number of cigarettes smoked by the family per day [63], and the other found that close and very close contact with smoking household members was strongly associated with TB (adjusted OR 9.31 [95% CI, 3.14–27.58]), while distant contact was not (adjusted OR 0.54 [95% CI, 0.25–1.16]) [62].



Note: The horizontal axis is on log scale

* The Gambia, Guinea Conakry, Guinea Bissau

Figure 4. Risk of Clinical TB Disease for Former Smoking Compared with Nonsmoking
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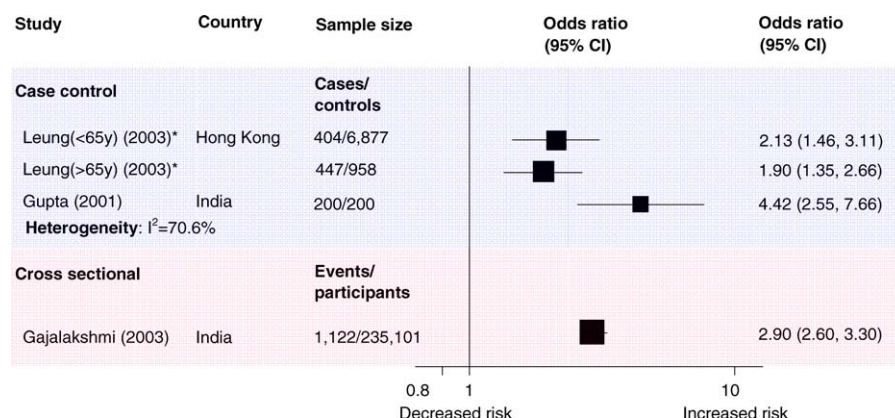
IAP and Clinical TB Disease

Only five studies of IAP and TB were identified (Figure 8) [36,42,48,65,66]. Of these, only two studies adjusted for tobacco smoking [42,66] while three others did not [36,48,65]. In each of the studies, IAP was assessed by questionnaire on cooking and heating with biomass fuels (wood or dung). Although three of the five studies reported a positive association between biomass use and TB disease, there was significant heterogeneity among the studies ($I^2 = 74.1\%$ in case-control studies) (Figure 8). We noted that in one study, houses were reportedly well ventilated and

therefore the impact of IAP might have been attenuated [48]. The sensitivity analyses are presented in Table 6.

Publication Bias

When we plotted the natural logarithms of the effect estimates against their standard errors using the methods described by Begg (Figure 9A) [9], we detected some slight asymmetry of effect estimates among small studies. We also noted that several large studies fell outside the projected lines of the funnel plot, indicating substantial variability among studies with small standard errors. When we repeated this



Note: The horizontal axis is on log scale

* No summary statistic given

Figure 5. Risk of Clinical TB Disease for Ever Smoking Compared with Nonsmoking
doi:10.1371/journal.pmed.0040020.g005

Table 3. Quality Assessment and Subgroup Analysis: Tobacco Smoking and TB Disease

Category	Measure or Outcome	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	<i>I</i> ²
Current smoking	Outcome	Pulmonary TB (16)	2.01	1.63–2.48	63.7%
		Any TB (4)	1.49	1.21–1.82	0%
	Adjustment for alcohol	Yes (8)	1.62	1.15–2.29	68.2%
		No (12)	1.95	1.60–2.39	55.2%
	Adjustment for socioeconomic status	Yes (9)	1.95	1.45–2.61	68.0%
		No (11)	1.79	1.44–2.22	52.5%
	Type of study	Cohort (1)	2.87	2.00–4.11	NA
		Case control (15)	1.70	1.41–2.04	54.4%
		Cross sectional (4)	2.30	1.51–3.50	50.2%
	Type of control among case-control studies	Population based (7)	1.77	1.40–2.25	50.5%
		Others (8)	1.60	1.17–2.18	62.3%
	Mode of diagnosis	Sputum exam included (14)	1.84	1.46–2.31	62.8%
		Others (6)	1.87	1.42–2.46	56.1%
Former smoking	Outcome	Pulmonary TB (6)	1.68	1.31–2.16	0%
		Any TB (3)	1.13	0.73–1.77	44.9%
	Adjustment for alcohol	Yes (5)	1.58	1.24–2.02	0%
		No (4)	1.36	0.79–2.36	53.8%
	Adjustment for socioeconomic status	Yes (4)	1.54	1.18–2.01	0%
		No (5)	1.44	0.90–2.31	51.7%
	Type of study	Cohort (1)	1.39	0.98–1.97	NA
		Case control (7)	1.56	1.09–2.23	47.3%
		Cross sectional (1)	1.74	0.53–5.71	NA
	Type of control among case-control studies	Population based (3)	1.33	0.69–2.57	66.5%
		Others (4)	1.79	1.27–2.53	0%
	Mode of diagnosis	Sputum exam included (7)	1.62	1.30–2.03	0%
		Others (2)	0.96	0.50–1.85	31.4%
Ever smoking	Outcome	Pulmonary TB (2)	3.28	2.25–4.76	53.6%
		Any TB (2)	2.00	1.55–2.57	0%
	Adjustment for alcohol	Yes (2)	2.00	1.55–2.57	0%
		No (2)	3.28	2.25–4.76	53.6%
	Adjustment for socioeconomic status	Yes (2)	3.28	2.25–4.76	53.6%
		No (2)	2.00	1.55–2.57	0%
	Type of study	Case control (3)	2.49	1.61–3.87	70.6%
		Cross sectional (1)	2.90	2.60–3.30	NA
	Mode of diagnosis	Sputum exam included (3)	2.48	1.61–3.87	70.6%
		Others (1)	2.90	2.60–3.30	NA

Not applicable (NA) indicated as appropriate; *I*² statistics can be computed only when there is more than one study.
doi:10.1371/journal.pmed.0040020.t003

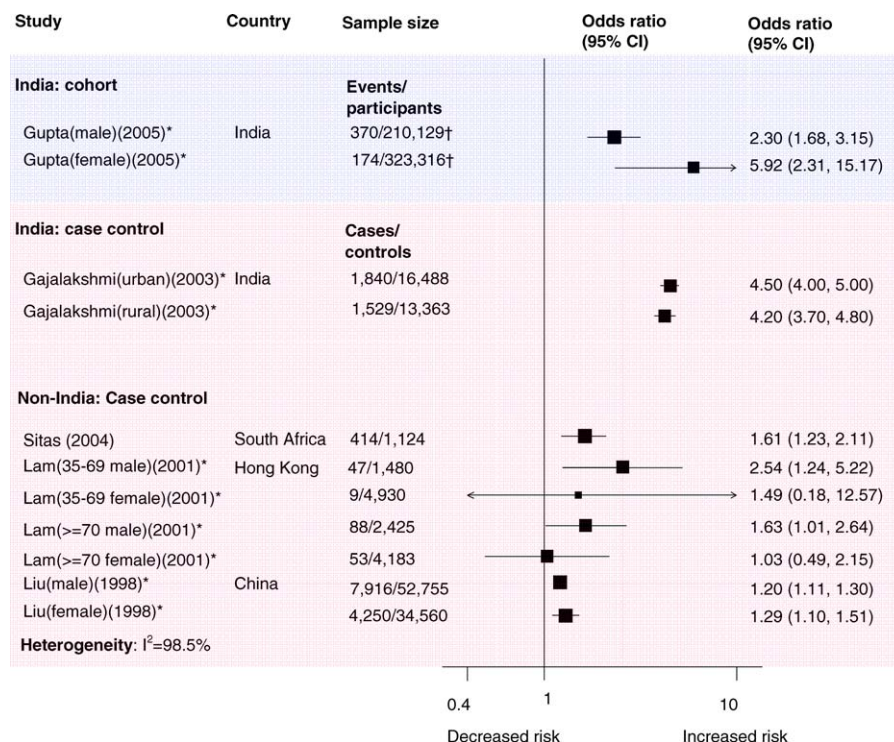
analysis excluding the five mortality studies, we found that the studies with small standard errors clustered within the funnel plot (Figure 9B). We found no evidence for substantial publication bias by either the Begg's test ($p = 0.256$) or the Egger's test ($p = 0.977$).

Discussion

This analysis shows that exposure to tobacco smoke is consistently associated with TB, regardless of the specific types of exposures and specific TB outcomes. Compared with people who do not smoke, smokers have an increased risk of a positive TST, of having active TB, and of dying from TB. Although there were fewer studies for passive smoking and IAP from biomass fuels, those exposed to these sources were found to have higher risks of active TB than those who are not exposed. An important finding of this study is the suggestion that the risk of TB among those exposed to passive smoking is especially high in children who are not normally at high risk for active disease. These findings support the hypothesis that exposure to respirable pollutants from

combustion of tobacco and biomass fuels increases the risk of both TB infection and TB disease.

In addition to the positive association demonstrated here, multiples lines of evidence support a causal relationship between combustion smoke and TB. A dose-response relationship has been demonstrated in most of the studies that have stratified on dose; in this meta-analysis, we found that the risk of TB increases with both daily dose of cigarettes and duration of smoking. There is also accumulating evidence for the biological plausibility of this association. Chronic exposure to tobacco as well as to a number of environmental pollutants impairs the normal clearance of secretions on the tracheobronchial mucosal surface and may thus allow the causative organism, *Mycobacterium tuberculosis*, to escape the first level of host defenses, which prevent bacilli from reaching the alveoli [67]. Smoke also impairs the function of pulmonary alveolar macrophages (AMs), which are not only the cellular target of *M. tuberculosis* infection but also constitute an important early defense mechanism against the bacteria; AMs isolated from the lungs of smokers have reduced phagocytic ability and a lower level of secreted



Note: The horizontal axis is on log scale

* No summary statistic given

† Person-years

Figure 6. Risk of Mortality Due to TB for Smoking Compared with Nonsmoking

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proinflammatory cytokines than do those from nonsmokers [68]. Recent work has suggested a novel mechanism for this effect; nicotine is hypothesized to act directly on nicotinic acetylcholine receptors on macrophages to decrease intracellular tumor necrosis factor- α production and thus impair intracellular killing of *M. tuberculosis* [69]. Wood smoke exposure in rabbits has also been shown to negatively affect

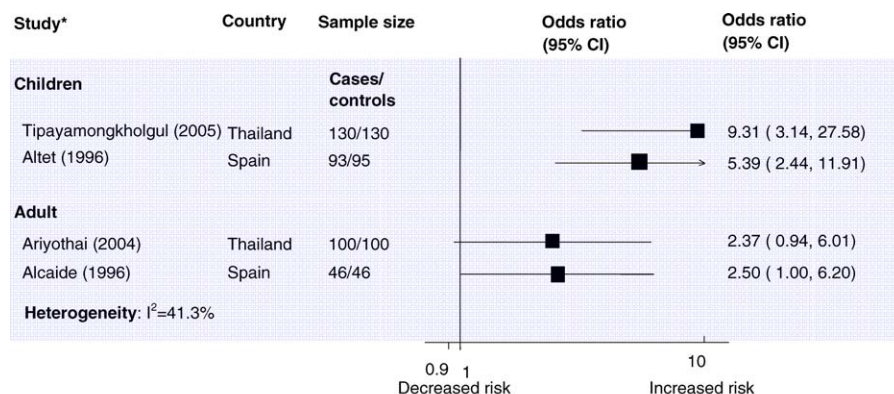
antibacterial properties of AMs, such as adherence to surfaces, ability to phagocytize bacteria, and intracellular bactericidal processes [70]. Boelaert and colleagues [71] have also proposed an alternative explanation for the impaired ability of macrophages from smokers to contain *M. tuberculosis* infection. These investigators noted that AMs from smokers have a markedly elevated iron content and that macrophage iron overload impairs defense against intracellular microorganisms through reduced production of both tumor necrosis factor- α and nitric oxide.

The available data support a causal link between smoke exposure and either an increased chance of acquiring TB or progression of TB to clinical disease. Our study shows that the risk of latent TB among smokers is quantitatively similar to their risk of active disease, which would suggest that much of the impact of smoking takes place during infection. At the same time, one case-control study selected TST-positive controls, thereby comparing patients who were TST positive and had clinical TB to people who were also TST positive but had not progressed to clinical TB [54]; that study also found a strong association between smoking and disease, suggesting that smoking may induce progression or reactivation disease in those infected. We included the outcome TB mortality in this study in order to investigate the association between smoke and TB occurrence rather than the association between smoke and TB treatment outcomes. The risk of death from TB among smokers was found to be somewhat higher than the risk of latent infection or disease, possibly because smoking has

Table 4. Quality Assessment and Subgroup Analysis: Tobacco Smoking and TB Mortality

Category	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	I^2
Outcome	Pulmonary TB (8)	2.00	1.14–3.49	98.7%
	Any TB (3)	2.32	1.43–3.77	76.0%
Adjustment for socioeconomic status	Yes (9)	2.55	1.82–3.56	90.7%
	No (2)	1.22	1.14–1.31	0%
Type of study	Cohort study (2)	3.31	1.34–8.16	71.3%
	Case control (9)	1.95	1.15–3.24	98.5%
Type of control among case-control studies	Population based (3)	1.29	1.13–1.48	55.7%
	Other (6)	2.84	2.06–3.91	84.8%
Type of smoking	Current smoking (3)	1.29	1.13–1.48	55.7%
	Ever smoking (8)	2.84	2.11–3.82	84.8%

doi:10.1371/journal.pmed.0040020.t004



Note: The horizontal axis is on log scale

*All studies are case control studies

Figure 7. Risk of Clinical TB Disease for Passive Smoking Exposure Compared with Nonexposure
doi:10.1371/journal.pmed.0040020.g007

been identified as a risk factor for poor TB treatment outcomes among those undergoing therapy [57,72,73].

There are several potential limitations to this study. First, our findings are based on the results of observational studies; we cannot, therefore, exclude the possibility of confounding by variables that may be associated with each of the exposures. The issue of confounding is particularly a concern in a meta-analysis of observational studies when effect sizes are relatively small, as was the case in the studies considered in this analysis [74]. We therefore performed a stratified analysis to explore the degree to which potential confounders may have influenced the findings. Among possible confounders, alcohol use is a known risk factor for TB and is closely associated with tobacco use in many populations. Those studies that adjusted for alcohol intake in a multivariable model found that the effect of smoking was reduced, but not eliminated. Those studies that controlled for the effect of alcohol were also less heterogeneous as a group than those that did not, a finding which suggests that some of the variability may have resulted from differences in alcohol consumption. Other risk factors that may confound the

association between smoking, passive smoking, and IAP and TB include socioeconomic status, gender, and age. Although it is impossible to fully exclude bias introduced by residual confounding, we found that the effects the exposures on TB remained after adjustment for these factors.

More than half of the studies in our review are case-control studies. These used different approaches to the selection of controls, including sampling from hospitals and clinics, from household members, and from the community. Since smoking is associated with a wide range of diseases, the choice of hospital- or clinic-based sampling may lead to over-representation of smokers among the controls, thereby biasing the results toward the null. Similarly, since people dwelling in the same household may share behavioral risk factors, controls chosen from households of smoking TB patients may have been more likely to smoke than would the general population [75]. When we compared the effect estimates for studies stratified on the basis of the control selection strategy, we found that studies that had not used population-based controls tended to report lower effect estimates, consistent with our expectation of a bias toward the null among studies that used hospital- and household-based controls.

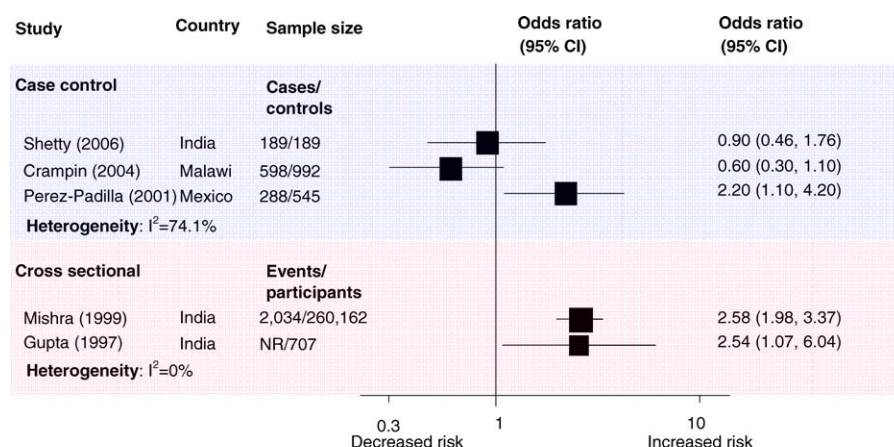
Other potential sources of bias include possible misclassification of both exposure and outcome status. The assessment of tobacco smoking relied on self-reported behavior, which may not have been accurate especially among those who consider smoking to be stigmatizing, such as women in some cultural settings. The exposure “current smoking” may also have been subject to reverse causation. Patients are often diagnosed with TB months or more after having first experienced symptoms of the disease, which may cause some patients to quit smoking. This is consistent with the finding of several studies that “former” smoking to be a stronger risk factor for TB than current smoking [34,42,48]. Nonetheless, since “former” smoking also included very distant smoking, both current and former smoking may underestimate the effect of smoking that had occurred just prior to the onset of disease. Similarly, misclassification of passive smoking and IAP may have introduced a bias toward the null in our analysis. The classification of passive smoking among children, for example, relied on parent reports, which may have been influenced by guilt or shame at having exposed the child

Table 5. Quality Assessment and Subgroup Analysis: Passive Smoking and TB Disease

Category	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	I^2
Outcome	Pulmonary TB (3)	3.33	1.93–5.72	13.5%
	Any TB (1)	9.31	3.14–27.58	NA
Adjustment for alcohol	Yes (1)	2.37	0.94–6.01	NA
	No (3)	4.83	2.40–9.73	42.4%
Adjustment for socioeconomic status	Yes (2)	3.80	1.80–8.04	35.6%
	No (2)	4.56	1.19–17.39	71.6%
Study population	Children (2)	6.52	3.44–12.36	0%
	Adults (2)	2.44	1.27–4.67	0%

Not applicable (NA) indicated as appropriate; I^2 statistics can be computed only when there is more than one study.

doi:10.1371/journal.pmed.0040020.t005



Note: The horizontal axis is on log scale

Figure 8. Risk of Clinical TB Disease for Indoor Air Pollution Exposure Compared with Nonexposure
doi:10.1371/journal.pmed.0040020.g008

to an agent suspected of causing disease. Most problematic among exposures was the classification of IAP; this usually relied on the proxy “use of biomass cooking fuel,” which probably only coarsely captured the actual exposure to inhaled smoke. For example, one study that found no association between biomass fuel use and TB noted that houses in the area were well ventilated, and thus actual exposure to inhaled smoke among those using biomass fuels was probably lower.

Misclassification of outcome may have also introduced bias into this analysis. For example, we included a large mortality study conducted in India in which the odds of death among urban male smokers was 4.5 times that of nonsmokers. Since diagnosis of TB in India relies heavily on radiographic findings, TB may be overdetected, especially among patients with pulmonary lesions—such as malignancies—that may be causally linked to smoking [76]. When we repeated our analysis excluding the two Indian mortality studies, the

heterogeneity among the remaining studies was reduced. Similarly, when the mortality studies were excluded from the funnel plot, there was much less variability among the studies with the smallest standard errors. Another possible source of outcome misclassification was suggested by Plant and colleagues [32], who noted that the frequency of small induration sizes among TSTs was higher among smokers than nonsmokers, suggesting that smokers may be less capable than nonsmokers of eliciting a vigorous skin test reaction and that latent TB infection in smokers may thus be underdetected when the 10 mm cutoff is used. Despite this possible limitation, we found that the two studies of latent infection that used 5 mm cutoffs for the TST [32,33] reported effects that were not statistically different from those that used 10 mm [30,31,34,35]. Finally, the diagnosis of TB in children is notoriously difficult; if children exposed to passive smoke were more likely to be successfully diagnosed with disease than those who were not, this might have introduced a bias that would explain the strong positive association between passive smoking and TB.

Although our evidence suggests that tobacco smoking is only a moderate risk factor in TB, the implication for global health is critical. Because tobacco smoking has increased in developing countries where TB is prevalent, a considerable portion of global burden of TB may be attributed to tobacco smoking (see Text S1 for an illustrative calculation of population-attributable fraction and attributable deaths in different regions of the world). More importantly, this association implies that smoking cessation might provide benefits for global TB control in addition to those for chronic diseases.

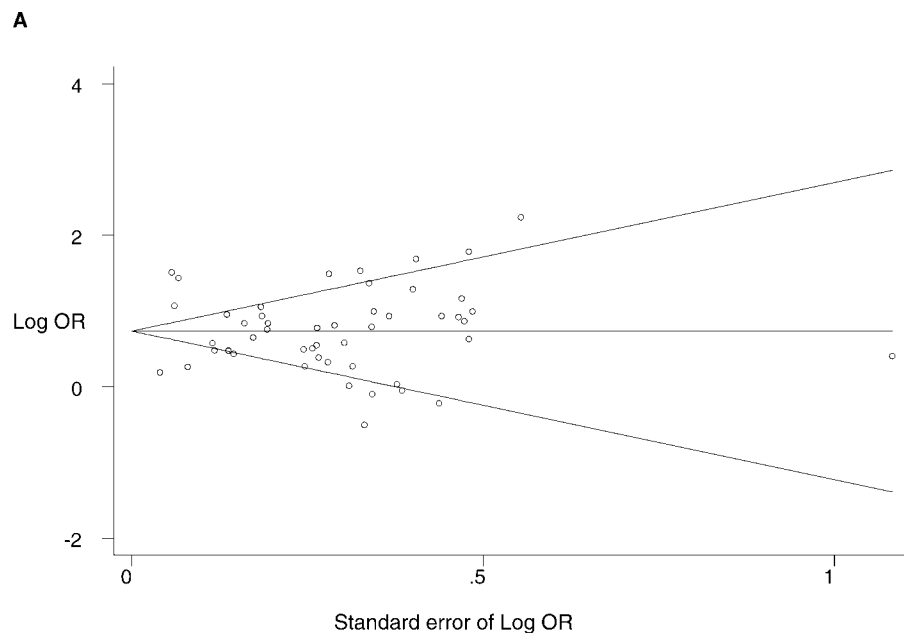
Despite heterogeneity in design, measurement, and quantitative effect estimates among the studies included in this analysis, we found consistent evidence for an increased risk of TB as a result of smoking, with more limited but consistent evidence for passive smoking and IAP as risk factors. These findings suggest that TB detection might benefit from information on exposure to respirable pollutants from sources such as smoking and biomass use, and that TB control might benefit from including interventions aimed at

Table 6. Quality Assessment and Subgroup Analysis: Indoor Air Pollution and TB Disease

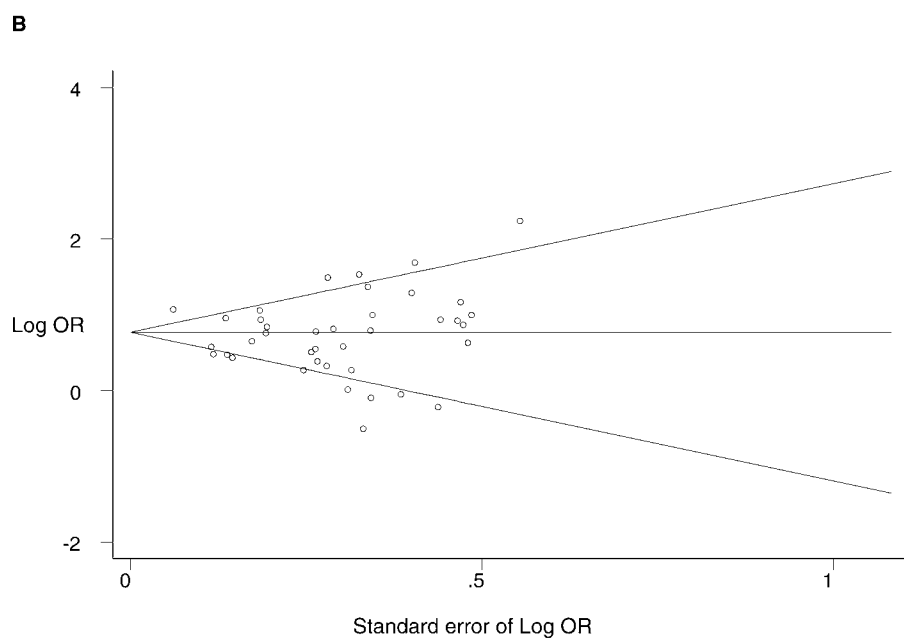
Category	Study Characteristics (Number of Studies)	Summary Estimate	95% CI	I^2
Outcome	Pulmonary TB (4)	1.95	1.20–3.16	63.7%
	Any TB (1)	0.60	0.30–1.10	NA
Adjustment for alcohol	Yes (1)	0.90	0.46–1.76	NA
	No (4)	1.73	0.88–3.41	82.1%
Adjustment for socioeconomic status	Yes (3)	1.81	0.98–3.35	75.6%
	No (2)	1.20	0.29–4.92	85.4%
Adjustment for tobacco smoking	Yes (2)	1.41	0.59–3.38	70.7%
	No (3)	1.59	0.61–4.15	88.1%
Type of study	Case control (3)	1.06	0.50–2.24	74.1%
	Cross sectional (2)	2.58	2.00–3.32	0%

Not applicable (NA) indicated as appropriate; I^2 statistics can be computed only when there is more than one study.

doi:10.1371/journal.pmed.0040020.t006



Log OR = natural log of odds ratio. Horizontal line = mean effect size



Log OR = natural log of odds ratio. Horizontal line = mean effect size

Figure 9. Begg's Funnel Plots with Pseudo 95% Confidence Limits

(A) Funnel plot for all studies.

(B) Funnel plot for all studies excluding mortality studies.

doi:10.1371/journal.pmed.0040020.g009

reducing tobacco and IAP exposure, especially among those at high risk for exposure to the infection.

Supporting Information

Text S1. Population-Attributable Fraction and Attributable Death Due to Tobacco Smoking on TB Mortality in Different Regions of the World

Found at doi:10.1371/journal.pmed.0040020.sd001 (33 KB DOC)

Alternative Language Abstract S1. Translation of the Article into Chinese by Hsien-Ho Lin

Found at doi:10.1371/journal.pmed.0040020.sd002 (64 KB PDF)

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Author contributions. HHL, ME, and MM conceived of the study and devised the search and analysis strategies. Electronic searches, expert contact, hand searches, retrieval of references were undertaken by HHL. Study selection criteria were developed by HHL and MM. Data synthesis and analysis were undertaken by HHL and MM. HHL wrote the first draft of this report and all authors contributed to the final draft.

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Editors' Summary

Background. Tobacco smoking has been identified by the World Health Organization as one of the leading causes of death worldwide. Smokers are at higher risk than nonsmokers for a very wide variety of illnesses, many of which are life-threatening. Inhaling tobacco smoke, whether this is active (when an individual smokes) or passive (when an individual is exposed to cigarette smoke in their environment) has also been associated with tuberculosis (TB). Many people infected with the TB bacterium never develop disease, but it is thought that people infected with TB who also smoke are far more likely to develop the symptoms of disease, and to have worse outcomes when they do.

Why Was This Study Done? The researchers were specifically interested in the link between smoking and TB. They wanted to try to work out the overall increase in risk for getting TB in people who smoke, as compared with people who do not smoke. In this study, the researchers wanted to separately study the risks for different types of exposure to smoke, so, for example, what the risks were for people who actively smoke as distinct from people who are exposed to smoke from others. The researchers also wanted to calculate the association between TB and exposure to indoor pollution from burning fuels such as wood and charcoal.

What Did the Researchers Do and Find? In carrying out this study, the researchers wanted to base their conclusions on all the relevant information that was already available worldwide. Therefore they carried out a systematic review. A systematic review involves setting out the research question that is being asked and then developing a search strategy to find all the meaningful evidence relating to the particular question under study. For this systematic review, the researchers wanted to find all published research in the biomedical literature that looked at human participants and dealt with the association between active smoking, passive smoking, indoor air pollution and TB. Studies were included if they were published in English, Russian, or Chinese, and included enough data for the researchers to calculate a number for the increase in TB risk. The researchers initially found 1,397 research studies but then narrowed that down to 38 that fit their criteria. Then specific pieces of data were extracted from each of those studies and in some

cases the researchers combined data to produce overall calculations for the increase in TB risk. Separate assessments were done for different aspects of “TB risk,” namely, TB infection, TB disease, and mortality from TB. The data showed an approximately 2-fold increase in risk of TB infection among smokers as compared with nonsmokers. The researchers found that all studies evaluating the link between smoking and TB disease or TB mortality showed an association, but they did not combine these data together because of wide potential differences between the studies. Finally, all studies looking at passive smoking found an association with TB, as did some of those examining the link with indoor air pollution.

What Do These Findings Mean? The findings here show that smoking is associated with an increased risk of TB infection, disease, and deaths from TB. The researchers found much more data on the risks for active smoking than on passive smoking or indoor air pollution. Tobacco smoking is increasing in many countries where TB is already a problem. These results therefore suggest that it is important for health policy makers to further develop strategies for controlling tobacco use in order to reduce the impact of TB worldwide.

Additional Information. Please access these Web sites via the online version of this summary at <http://dx.doi.org/10.1371/journal.pmed.0040020>

- The World Health Organization (WHO)'s Tobacco Free Initiative provides resources on research and policy related to tobacco control, its network of initiatives, and other relevant information
- WHO also has a tuberculosis minisite
- The US National Library of Medicine's MedLinePlus provides a set of links and resources about smoking, including news, overviews, recent research, statistics, and others
- The Health Consequences of Smoking: A Report of the Surgeon General provides information on the health consequences of smoking
- Tobacco Country Profiles provides information on smoking in different countries